A NOVEL NQO1 SPECIFIC ANTI-TUMOR AGENT, SBSC-S3001, SELECTIVELY REGRESSES THE GROWTH OF TUMORS WITH HIGH NQO1 EXPRESSION

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Background NAD(P)H-quinone oxidoreductase 1 (NQO1) is a cytosolic two-electron oxidoreductase overexpressed in many types of cancers, including breast cancer, pancreatic cancer, colorectal cancer, cholangiocarcinoma, uterine cervical cancer, melanoma, and lung cancer. Up-regulation of NQO1 protects cells from oxidative stress and various cytotoxic quinones and is associated with late clinical stage, poor prognosis and lymph node metastasis. NQO1 overexpression is associated with increased numbers of cancer stem cells, the source of distant metastasis.

Methods In vitro cytotoxicity was determined by sulforhodamine B (SRB) assay in cancer cells with high NQO1 expression and CRISPR-mediated NQO1 knockout cells. The effect of SBSC-S3001 on the energy metabolism pathway was evaluated by western blot analysis of metabolism associated proteins from NQO1-overexpressed cancer cells treated with the compound for 24 hours. In vivo anti-tumor activity was evaluated in MC38 syngeneic and DLD-1 orthotopic mice models. SBSC-S3001 exhibited selective cytotoxicity in cancer cells with high expression of NQO1 in a dose-dependent manner. The cytotoxicity was observed in both normoxia and hypoxia conditions, correlating with the energy metabolism, mitochondrial biogenesis, and cancer proliferative pathways. Also, stronger cytotoxicity was observed in NQO1-overexpressed cancer cells treated with SBSC-S3001 compared to beta-lapachone and analogue treatments.

Results SBSC-S3001 effectively inhibited the growth of syngeneic and orthotopic tumors when administered as a monotherapy. SBSC-S3001 treatment associated with reduction in key enzymes of the glycolytic pathway (LDHα, GAPDH and HIF-1α), and increase in levels of mitochondrial oxidative phosphorylation (OXPHOS) complex.

Conclusions Treatment of SBSC-S3001, a novel, NQO1-specific substrate reduces HIF-1α and key enzymes associated with glycolysis and suppresses the growth of tumors overexpressing NQO1. Further characterization of SBSC-S3001 as a novel metabolic anti-cancer agent for cancers with NQO1 overexpression is warranted.

Ethics Approval The study was approved by Samyang Biopharmaceuticals Institution’s Ethics Board, approval number SYAU2031.

REFERENCES
2. Ma, Y. et al. NQO1 overexpression is associated with poor prognosis in squamous cell carcinoma of the uterine cervix. BMC Cancer 2014;14: 414